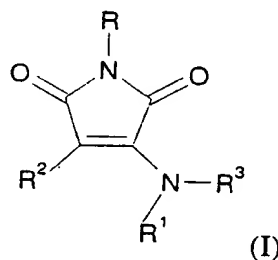


## Claims

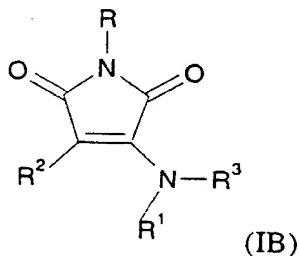
1. A method for the treatment of conditions associated with a need for inhibition of GSK-3, such as diabetes, dementias such as Alzheimer's disease and manic depression which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I):



or a pharmaceutically acceptable derivative thereof, wherein:

- R is hydrogen, alkyl, aryl, or aralkyl;  
 R<sup>1</sup> is hydrogen, alkyl, aralkyl, hydroxyalkyl or alkoxyalkyl;  
 R<sup>2</sup> is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl;  
 R<sup>3</sup> is hydrogen, substituted or unsubstituted alkyl, cycloalkyl, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl or aralkyl wherein the aryl moiety is substituted or unsubstituted; or,  
 R<sup>1</sup> and R<sup>3</sup> together with the nitrogen to which they are attached form a single or fused, optionally substituted, saturated or unsaturated heterocyclic ring;  
 to a human or non-human mammal in need thereof.

A compound of formula (IB),



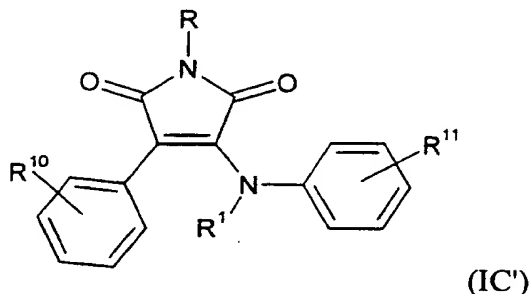
or a derivative thereof, wherein:

- R is hydrogen, alkyl, aryl, or aralkyl;  
 R<sup>1</sup> is hydrogen, alkyl, aralkyl, hydroxyalkyl or alkoxyalkyl;  
 R<sup>2</sup> is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl;  
 R<sup>3</sup> is hydrogen, substituted or unsubstituted alkyl, cycloalkyl, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl or aralkyl wherein the aryl moiety is substituted or unsubstituted; or,

*contd.*  
*a<sup>1</sup>*

R<sup>1</sup> and R<sup>3</sup> together with the nitrogen to which they are attached form a single or fused, optionally substituted, saturated or unsaturated heterocyclic ring; with the proviso that formula (IB) does not include the compounds contained in List B.

- 5 3. A compound according to claim 2 of formula (IC')



wherein;

R and R<sup>1</sup> are as defined in relation to formula (I) in claim 1;

R<sup>10</sup> represents hydrogen or one or more substituents, suitably up to three, selected from the list consisting of: alkoxy carbonyl, alkoxy alkyl, perfluoroalkyl, perfluoroalkylS-, perfluoroalkylO-, phenyl(di-C<sub>1-6</sub>alkoxy)C-, benzoyl, C<sub>1-6</sub>alkylSO<sub>2</sub>-, -[(CH=CH)<sub>2</sub>]-, phenyl, nitro, -OCH<sub>2</sub>O-, benzyloxy, phenoxy, halo, hydroxy, alkyl, alkoxy, amino, mono- or di-alkyl amino or thioalkyl;

R<sup>11</sup> represents hydrogen or one or more substituents, suitably up to three, selected from the list consisting of: substituted or unsubstituted C<sub>1-6</sub>alkyl, phenyl, benzyl, substituted or unsubstituted C<sub>1-6</sub>alkylS-, halo, hydroxy, substituted or unsubstituted C<sub>1-6</sub>alkoxy, substituted or unsubstituted phenoxy, indolyl, naphthyl, carboxy, C<sub>1-6</sub>alkoxy carbonyl, benzyloxy, phenoxy, pentafluorophenoxy, nitro, substituted or unsubstituted carbamoyl, substituted or unsubstituted C<sub>1-6</sub>alkyl carbonyl, benzoyl, cyano, perfluoroC<sub>1-6</sub>alkylSO<sub>2</sub>-, C<sub>1-6</sub>alkylNH<sub>2</sub>SO<sub>2</sub>-, oxazolyl, substituted or unsubstituted phenylS-, C<sub>1-6</sub>alkylpiperazinyl-, C<sub>1-6</sub>alkyl carbonyl piperazinyl-, 1,2,3-thiadiazolyl, pyrimidin-2-yloxy, N-[pyrimidin-2-yl]-N-methylamino, phenylamino, C<sub>1-6</sub>alkylsulphonylamino, N-morpholinyl carbonyl, cyclohexyl, adamantyl, trityl, substituted or unsubstituted C<sub>1-6</sub>alkenyl, perfluoroC<sub>1-6</sub>alkyl, perfluoroC<sub>1-6</sub>alkoxy, perfluoroC<sub>1-6</sub>alkylS-, aminosulphonyl, morpholino, (diC<sub>1-6</sub>alkyl)amino, C<sub>1-6</sub>alkylCONH-, (diC<sub>1-6</sub>alkoxy)phenyl(CH<sub>2</sub>)<sub>n</sub>NHC(O)CH(phenyl)S- where n is 1 to 6, and C<sub>1-6</sub>alkylCON(C<sub>1-6</sub>alkyl)-, thiazolidinedionylC<sub>1-6</sub>alkyl, phenylCH(OH)-, substituted or unsubstituted piperazinylC<sub>1-6</sub>alkoxy, substituted or unsubstituted benzoylamino; or -(CH<sub>2</sub>)<sub>x</sub>-, -SCH=N-, -SC(C<sub>1-6</sub>alkyl)=N-, -OCF<sub>2</sub>O-, -[CH=CHC(O)O]-, -[N=CH-CH=CH]-, -CH=N-NH-, -CH=CH-NH-, -OC(NHC<sub>1-6</sub>alkyl)=N-, -OC(O)NH-, -C(O)NMeC(O)-, -C(O)NHC(O)-, -(CH<sub>2</sub>)<sub>x</sub>C(O)-, -N=N-NH-, -N=C(C<sub>1-6</sub>alkyl)O-, -O(CH<sub>2</sub>)<sub>x</sub>O-, -(CH<sub>2</sub>)<sub>x</sub>SO<sub>2</sub>(CH<sub>2</sub>)<sub>y</sub>-, and -N(C<sub>1-6</sub>alkyl carbonyl)(CH<sub>2</sub>)<sub>x</sub>-, where x and y are independently 1 to 4;

with the proviso that (IC') does not include:  
3-phenylamino-4-phenyl-1H-pyrrole-2,5-dione;

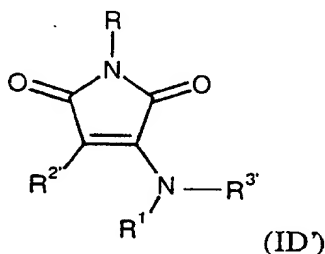
contd.  
a<sup>1</sup>

~~1-(4-methylphenyl)-3-[(4-methylphenyl)amino]-4-phenyl-1H-pyrrole-2,5-dione;  
3-(4-methylphenyl)-1-phenyl-4-(phenylamino)-1H-pyrrole-2,5-dione;  
1,3-bis(4-methylphenyl)-4-[(4-methylphenyl)amino]-1H-pyrrole-2,5-dione, or;  
3-(4-nitrophenyl)-1-phenyl-4-phenylamino-1H-pyrrole-2,5-dione.~~

4. A compound according to claim 3 wherein  
5 R and R<sup>1</sup> each represent hydrogen, and;  
R<sup>10</sup> and R<sup>11</sup> are defined as follows:  
when R<sup>10</sup> is 4-Cl, then R<sup>11</sup> is 3-Cl, 3-Br, or 4-CH<sub>2</sub>SO<sub>2</sub>NHMe;  
when R<sup>10</sup> is 2-OMe, then R<sup>11</sup> is 4-OMe or 3,5-di-F;  
when R<sup>10</sup> is 2-F, then R<sup>11</sup> is 3,5-di-F;  
10 when R<sup>10</sup> is 3-F, then R<sup>11</sup> is 4-(CH<sub>2</sub>)<sub>3</sub>CO<sub>2</sub>H;  
when R<sup>10</sup> is 2,3-di-F-Ph, then R<sup>11</sup> is 3,5-di-F.

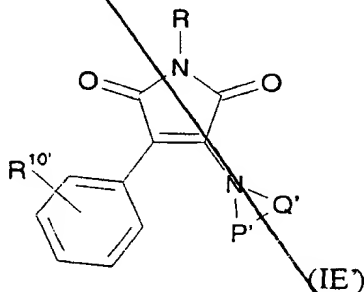
Amen.  
a<sup>2</sup>

5. A compound according to claim 2 of formula (ID')



wherein R and R<sup>1</sup> are as defined in relation to formula (I) in claim 1;  
R<sup>2</sup>' is phenyl, substituted phenyl or indolyl;  
R<sup>3</sup>' is hydrogen, alkyl, cycloalkyl, phenyl, substituted phenyl, C<sub>1-6</sub> alkylphenyl  
20 wherein the phenyl group is optionally substituted, alkoxyalkyl, substituted or  
unsubstituted heterocyclyl, with the proviso that formula (ID') does not include the  
compounds contained in List D'

6. A compound according to claim 2 of formula (IE')



wherein R is as defined in relation to formula (I) in claim 1;

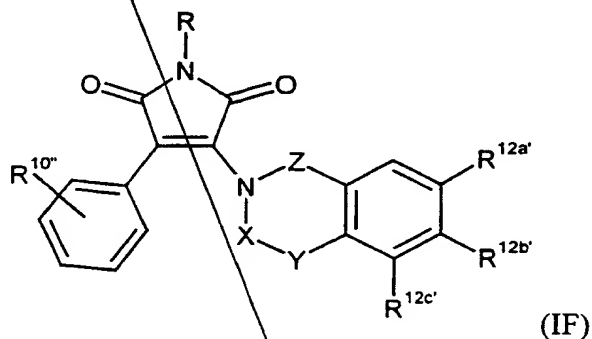
contd.  
a<sup>2</sup>

R<sup>10'</sup> represents hydrogen or one or more, suitably up to three, substituents selected from the list consisting of: alkoxy, halo, and nitro;

P'-Q' represents -(CH<sub>2</sub>)<sub>a</sub>O(CH<sub>2</sub>)<sub>b</sub>-, -(CH<sub>2</sub>)<sub>a</sub>S(CH<sub>2</sub>)<sub>b</sub>-, -(CH<sub>2</sub>)<sub>c</sub>-, -(CH<sub>2</sub>)<sub>d</sub>CH(G)(CH<sub>2</sub>)<sub>e</sub>-, -(CH<sub>2</sub>)<sub>a</sub>N(ZZ)(CH<sub>2</sub>)<sub>b</sub>-, where a, b, d, and e are independently 1 to 4, c is 1 to 6, ZZ is hydrogen, alkyl, aryl, or alkylcarbonyl, and G is alkyl, amido, hydroxyalkyl, aralkyl, or hydroxy, with the proviso that (IE') does not include:

3-phenyl-4-piperidin-1-yl-pyrrole-2,5-dione;  
3-(4-methylpiperazin-1-yl)-4-phenyl-pyrrole-2,5-dione;  
3-(4-ethylpiperazin-1-yl)-4-phenyl-pyrrole-2,5-dione;  
3-(4-chlorophenyl)-4-(4-methyl-piperazin-1-yl)-pyrrole-2,5-dione;  
3-(4-methylphenyl)-4-(4-morpholinyl)-1-phenyl-1H-pyrrole-2,5-dione  
3-phenyl-4-(4-methylpiperazino)-pyrrole-2,5-dione;  
3-phenyl-4-(4-phenylpiperazino)-pyrrole-2,5-dione;  
1-methyl-3-phenyl-4-(4-phenylpiperazino)-pyrrole-2,5-dione;  
1-ethyl-3-phenyl-4-(4-chlorophenylpiperazino)-pyrrole-2,5-dione;  
1-allyl-3-phenyl-4-(4-methylpiperazino)-pyrrole-2,5-dione, and;  
1,3-diphenyl-4-piperidino-pyrrole-2,5-dione.

7. A compound according to claim 2 of formula (IF)



wherein R is as defined in relation to formula (I) in claim 1;

R<sup>10''</sup> is one or more, suitably up to three, substituents selected from the list consisting of perfluoroalkyl, halo, nitro, alkoxy, arylcarbonyl, alkyl;

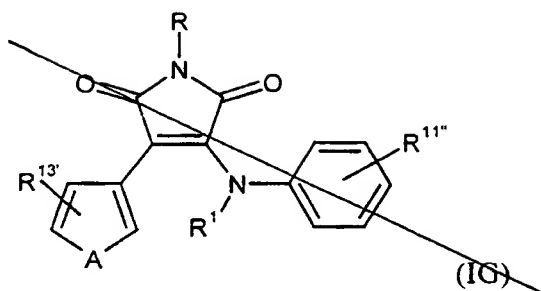
Z is a bond or an alkylene chain;

-X-Y- is -CH=N-, -(CH<sub>2</sub>)<sub>t</sub>-, -(CH<sub>2</sub>)<sub>u</sub>CH(U)-, -(U)CH(CH<sub>2</sub>)<sub>u</sub>-, -CH=CH-, -(CH<sub>2</sub>)<sub>v</sub>C(alkyl)<sub>2</sub>-, -C(O)C(alkyl)<sub>2</sub>-, -C(O)O-, where t, u, and v are independently 1 to 4, and U is alkyl, carboxy, alkoxycarbonyl, hydroxyalkyl, and amido;

R<sup>12a'</sup>, R<sup>12b'</sup>, and R<sup>12c'</sup> are each independently hydrogen, nitro, alkoxy, 4-ethylpiperazin-1-yl, 4-BOC-piperazin-1-yl, 4-methyl-piperazin-1-yl, 4-methyl-piperazin-1-yl, halo, alkyl, piperazin-1-yl, perfluoroalkyl, and alkylsulphonylamino.

8. A compound according to claim 2 of formula (IG)

contd.  
a<sup>2</sup>



wherein R and R<sup>1</sup> are as defined in relation to formula (I) in claim 1;

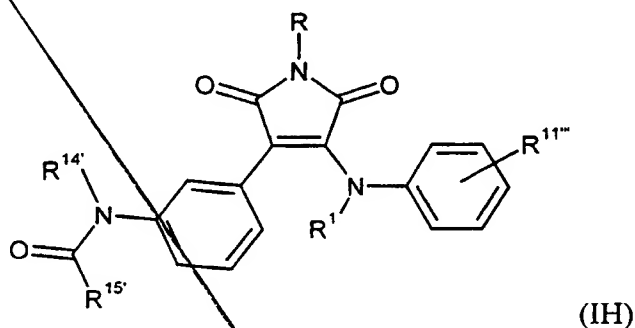
A is N(alkyl), oxygen, or sulphur.

Examples of A are N(methyl), oxygen, and sulphur.

Preferably, A is sulphur.

R<sup>11''</sup> is one or more, suitably up to three, substituents selected from the group consisting of hydrogen, halo, alkyl, alkylthio, -S-CH=N-, phenoxy, -(CH<sub>2</sub>)<sub>w</sub>-, hydroxy, carboxy, -O(CH<sub>2</sub>)<sub>x</sub>O-, hydroxyalkyl, and alkylaminosulphonylalkyl, where w and x are independently 1 to 4.

9. A compound according to claim 2 of formula (IH)



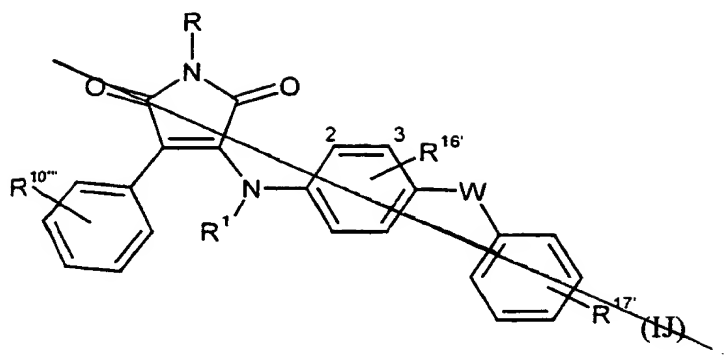
wherein R and R<sup>1</sup> are as defined in relation to formula (I) in claim 1;

R<sup>11'''</sup> is -[(CH<sub>2</sub>)<sub>aa</sub>]-, where aa is 1 to 4;

R<sup>14'</sup> is hydrogen;

R<sup>15'</sup> is alkyl, unsubstituted or substituted phenylamino, unsubstituted or substituted phenylalkylamino, cyclohexylamino, alkenylamino, phenyl, benzyl, styryl, or alkylamino.

10. A compound according to claim 2 of formula (IJ)



wherein R and R<sup>1</sup> are as defined in relation to formula (I) in claim 1;

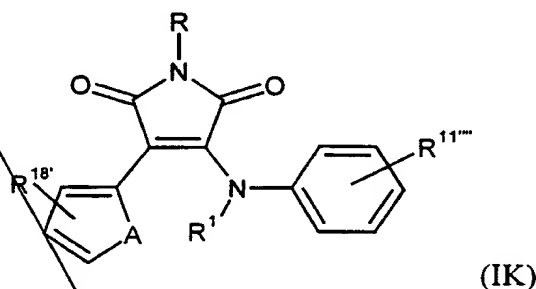
R<sup>10'''</sup> represents one or more, suitably up to three, substituents independently selected from alkoxy or halo;

R<sup>16'</sup> represents one or more, suitably up to three, substituents independently selected from hydrogen, carboxy, alkoxycarbonyl, or alkylaminocarbonyl;

R<sup>17'</sup> represents one or more, suitably up to three, substituents independently selected from carboxy, alkoxycarbonyl, halo, alkylaminocarbonyl, nitro, or hydrogen;

W is sulphur, oxygen, or substituted or unsubstituted NH.

11. A compound according to claim 2 of formula (IK)



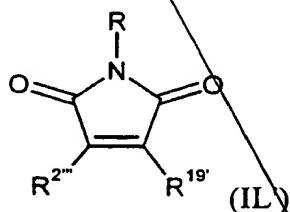
wherein R and R<sup>1</sup> are as defined in relation to formula (I) in claim 1;

R<sup>11'''</sup> represents one or more, suitably up to three, substituents independently selected from halo and hydroxy;

R<sup>18'</sup> represents one or more, suitably up to three, substituents independently selected from hydrogen, alkyl, and  $-(CH=CH)_2-$ ;

A is sulphur.

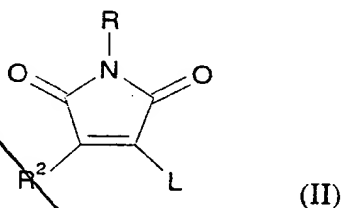
12. A compound according to claim 2 of formula (IL')



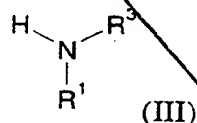
contd.  
a<sup>2</sup>

wherein R is as defined in relation to formula (I) in claim 1;  
R<sup>2''</sup> is unsubstituted or substituted heterocyclyl or unsubstituted or substituted aryl;  
R<sup>19'</sup> is unsubstituted or substituted heterocyclyl, or a quaternised salt thereof, with the proviso that formula (IL') does not include the compounds contained in List L'.

13. A process for the preparation of a compound of the invention which process comprises reaction of a compound of formula (II):



wherein R and R<sup>2</sup> are as defined in formula (I) in claim 1 and L is a leaving group, with a compound of formula (III):



wherein R<sup>1</sup> and R<sup>3</sup> are as defined in formula (I) in claim 1; and thereafter, if required, carrying out one or more of the following optional steps:

- (i) converting a compound of formula (I) to a further compound of formula (I);
- (ii) removing any necessary protecting group;
- (iii) preparing an appropriate derivative of the compound so formed.

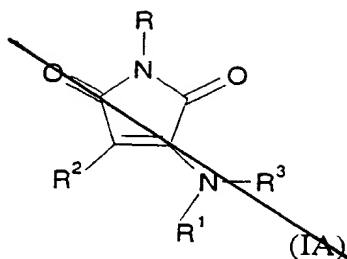
14. A compound of formula (I) according to claim 1 for use in conditions associated with a need for inhibition of glycogen synthase kinase-3.

15. Use of a compound of formula (I) according to claim 1 for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of glycogen synthase kinase-3.

~~16. A compound of formula (IA)~~

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amen.  
a<sup>3</sup>

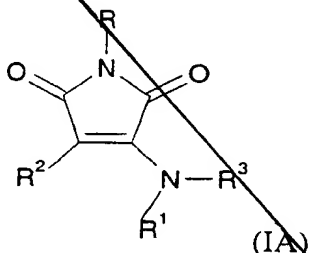
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a<sup>3</sup>



wherein

R is hydrogen, alkyl, aryl, or aralkyl;  
 R<sup>1</sup> is hydrogen, alkyl, aralkyl, hydroxyalkyl or alkoxyalkyl;  
 R<sup>2</sup> is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl;  
 R<sup>3</sup> is hydrogen, substituted or unsubstituted alkyl, cycloalkyl, alkoxyalkyl,  
 substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl or aralkyl  
 wherein the aryl moiety is substituted or unsubstituted; or,  
 R<sup>1</sup> and R<sup>3</sup> together with the nitrogen to which they are attached form a single or fused,  
 optionally substituted, saturated or unsaturated heterocyclic ring;  
 or a pharmaceutically acceptable derivative thereof, for use as an active therapeutic  
 substance, with the proviso that formula (IA) does not include the compounds contained  
 in List A.

17. A pharmaceutical composition which comprises a compound of formula (IA)



wherein

R is hydrogen, alkyl, aryl, or aralkyl;  
 R<sup>1</sup> is hydrogen, alkyl, aralkyl, hydroxyalkyl or alkoxyalkyl;  
 R<sup>2</sup> is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl;  
 R<sup>3</sup> is hydrogen, substituted or unsubstituted alkyl, cycloalkyl, alkoxyalkyl,  
 substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl or aralkyl  
 wherein the aryl moiety is substituted or unsubstituted; or,  
 R<sup>1</sup> and R<sup>3</sup> together with the nitrogen to which they are attached form a single or fused,  
 optionally substituted, saturated or unsaturated heterocyclic ring;  
 or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable  
 carrier, with the proviso that formula (IA) does not include the compounds contained in  
 List A.



18. A method for the treatment and/or prophylaxis of mood disorders in a mammal, which method comprises the administration of a pharmaceutically acceptable amount of a GSK-3 inhibitor.

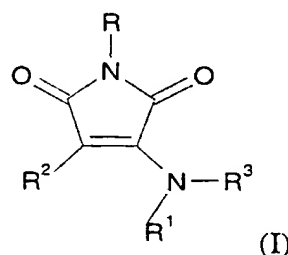
19. A method for the treatment and/or prophylaxis of neurotraumatic diseases in a mammal, which method comprises the administration of a pharmaceutically acceptable amount of a GSK-3 inhibitor.

20. A method for the treatment and/or prophylaxis of cancer, in a mammal, which method comprises the administration of a pharmaceutically acceptable amount of a GSK-3 inhibitor.

21. A method for the treatment and/or prophylaxis of hair-loss, in a mammal, which method comprises the administration of a pharmaceutically acceptable amount of a GSK-3 inhibitor.

22. Use of a GSK-3 inhibitor for the manufacture of a medicament for the treatment and/or prophylaxis of mood disorders, schizophrenia, neurotraumatic diseases, cancer or hair-loss.

23. A compound of formula (I)



or a derivative thereof, wherein:

R is hydrogen, alkyl, aryl, or aralkyl;

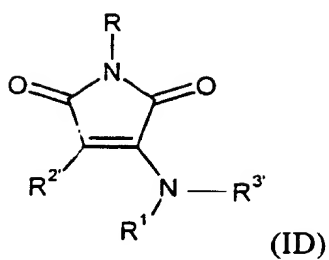
R¹ is hydrogen, alkyl, aralkyl, hydroxyalkyl or alkoxyalkyl;

R² is substituted or unsubstituted aryl or substituted or unsubstituted heterocyclyl;

R³ is hydrogen, substituted or unsubstituted alkyl, cycloalkyl, alkoxyalkyl,

substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl or aralkyl wherein the aryl moiety is substituted or unsubstituted; or,

R¹ and R³ together with the nitrogen to which they are attached form a single or fused, optionally substituted, saturated or unsaturated heterocyclic ring; with the proviso that the compounds of formula (ID)



wherein R and R<sup>1</sup> are as defined in relation to formula (I);

R<sup>2'</sup> is phenyl, substituted phenyl or indolyl;

5 R<sup>3'</sup> is hydrogen, alkyl, cycloalkyl, phenyl, substituted phenyl, C<sub>1-6</sub> alkylphenyl  
wherein the phenyl group is optionally substituted, alkoxyalkyl, substituted or  
unsubstituted heterocyclyl;  
are excluded.